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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/574,860	04/06/2006	Shigeto Kawai	053466-0414	8677

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EXAMINER	
GUSSOW, ANNE	
ART UNIT	**PAPER NUMBER**
1643	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/574,860	KAWAI ET AL.	
	Examiner	Art Unit	
	Anne M. Gussow	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 June 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) *1-14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *06 April 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/5/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *sequence alignment*.

DETAILED ACTION

1. Applicant's election with traverse of Group II, claims 15-21, and the species of breast cancer, in the reply filed on June 12, 2007 is acknowledged. The traversal is on the ground(s) that the treatment of solid cancers with an anti-HM1.24 antibody is a special technical feature shared by all of the claims and that there would not be a search burden for the examiner to search all solid tumor types. This is not found persuasive because as set forth in the restriction requirement, Hirano, et al. (US PG PUB 2001/0051710, as cited in the previous action) teach an antibody that binds to a protein having the identical sequence as the instant SEQ ID No. 2, thus the technical feature of the antibody shared by all the claims is not a special technical feature. Regarding the search burden, each of the cancer types in claim 15 involves a different organ system, different cell types, and different cellular mechanisms therefore there would be a search burden to search all of the cancer types.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 1-14 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on June 12, 2007.

3. Claims 15-21 are under examination.

4. In addition to the elected species of breast cancer, the species of ovarian cancer has also been searched for this Office Action.

Priority

5. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 365(c) as follows:

The certified copies of the priority documents, both PCT/JP04/15205 and Japan 2003-352819 have been filed in a foreign language and are not accompanied by a certified English translation. To receive priority to the filing date of these documents, a certified English translation is required.

Thus, for art purposes in this Office Action the priority date of the application is April 6, 2006.

Information Disclosure Statement

6. The information disclosure statement (IDS) submitted on September 5, 2006 has been fully considered by the examiner and an initialed copy of the IDS is included in the mailing of this office action.

Oath/Declaration

7. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:
It does not identify the citizenship of each inventor. The citizenship of the inventors is listed as a nationality (Japanese) instead of a country (Japan).

Specification

8. The abstract of the disclosure is objected to because it contains legal phraseology. Correction is required. See MPEP § 608.01(b).

Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

9. The disclosure is objected to because of the following informalities: the specification contains typographical errors, for example, on page 5 line 20 "patters" should read "patterns".

Appropriate correction is required for all errors throughout.

Claim Rejections - 35 USC § 112

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 15-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a.) Claims 15-21 are indefinite for reciting the phrase "antibody activity" in claim 15. It is not clear what the activity of the antibody is supposed to be, is this a catalytic antibody?

b.) Claim 15 recites the limitation "said agent" in line 1. There is insufficient antecedent basis for this limitation in the claim.

c.) Claim 18 recites the limitation "the framework region" in line 3. There is insufficient antecedent basis for this limitation in the claim.

12. Claims 15-21 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the

steps. See MPEP § 2172.01. The omitted steps are: an administering step or a detecting step or a treatment step.

13. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

14. Claims 15-21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for treating a solid tumor by administering an antibody that specifically binds to a protein having the amino acid sequence as set forth in SEQ ID No. 2 *in vitro*, does not reasonably provide enablement for a method of treating a solid tumor by administering an antibody that contains only one complementarity determining region (CDR), or a method of treating a solid tumor *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 1 12, first paragraph, have been described by the court in In re Wands, 8 USPQ2d 1400 (CA FC 1988).

> Wands states on page 1404,
> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The claims are broadly drawn to a therapeutic method for solid tumors comprising as an active ingredient, an antibody that specifically binds to a protein having the amino acid sequence set forth in SEQ ID No. 2 or an antibody fragment that maintains the antibody activity, in which said antibody is a humanized antibody comprising the complementarity determining region of a mouse antibody and the framework region and the constant region of a human antibody.

The specification discloses an anti-HM1.24 antibody and humanized anti-HM1.24 antibody (example 2, page 39). The specification discloses measurement of ADCC activity of the anti-HM1.24 antibody on human PBMC cells (example 12 and figure 13). The specification does not disclose treatment of solid tumors in vivo. The specification does not disclose treatment with an antibody containing fewer than 6 CDRs (3 heavy chain and 3 light chain).

It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable

regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc Natl Acad Sci, 1982. Vol. 79, page 1979). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. MacCallum et al. (Journal of Molecular Biology, 1996. Vol. 262, pages 732-745) analyzed many different antibodies for interactions with antigen and state that although CDR3 of the heavy and light chain dominate, a number of residues outside the standard CDR definitions make antigen contacts (see page 733, right column) and non-contacting residues within the CDRs coincide with residues as important in defining canonical backbone conformations (see page 735, left column). Pascalis et al. (Journal of Immunology, 2002. Vol. 169, pages 3076-3084) demonstrate that grafting of the CDRs into a human framework was performed by grafting CDR residues and maintaining framework residues that were deemed essential for preserving the structural integrity of the antigen binding site (see page 3079, right column). Although abbreviated CDR residues were used in the constructs, some residues in all 6 CDRs were used for the constructs (see page 3080, left column). The fact that not just one CDR is essential for antigen binding or maintaining the conformation of the antigen binding site, is underscored by Casset et al. (Biochemical and Biophysical Research Communications, 2003. Vol. 307, pages 198-205) which constructed a peptide mimetic of an anti-CD4 monoclonal antibody binding site by rational design and the peptide was designed with 27 residues formed by

residues from 5 CDRs (see entire document). Casset et al. also states that although CDR H3 is at the center of most if not all antigen interactions, clearly other CDRs play an important role in the recognition process (page 199, left column) and this is demonstrated in this work by using all CDRs except L2 and additionally using a framework residue located just before the H3 (see page 202, left column). Vajdos et al. (Journal of Molecular Biology, 2002. Vol. 320, pages 415-428) additionally state that antigen binding is primarily mediated by the CDRs more highly conserved framework segments which connect the CDRs are mainly involved in supporting the CDR loop conformations and in some cases framework residues also contact antigen (page 416, left column). Holm, et al. (Molecular Immunology, 2007. Vol. 44, pages 1075-1084) describes the mapping of an anti-cytokeratin antibody where although residues in the CDR3 of the heavy chain were involved in antigen binding unexpectedly a residue in CDR2 of the light chain was also involved (abstract). Chen et al. (Journal of Molecular Biology, 1999. Vol. 293, pages 865-881) describe high affinity variant antibodies binding to VEGF wherein the results show that the antigen binding site is almost entirely composed of residues from heavy chain CDRs, CDR-H1, H2, H3 (page 866). Wu, et al. (Journal of Molecular Biology, 1999. Vol. 294, pages 151-162) state that it is difficult to predict which framework residues serve a critical role in maintaining affinity and specificity due in part to the large conformational change in antibodies that accompany antigen binding (page 152 left column) but certain residues have been identified as important for maintaining conformation.

Regarding treatment *in vivo* compared to *in vitro*, those of skill in the art recognize that in vitro assays and or cell-cultured based assays are generally useful to observe basic physiological and cellular phenomenon such as screening the effects of potential drugs. However, clinical correlations are generally lacking. The greatly increased complexity of the in vivo environment as compared to the very narrowly defined and controlled conditions of an in- vitro assay does not permit a single extrapolation of in vitro assays to human diagnostic efficacy with any reasonable degree of predictability. In vitro assays cannot easily assess cell-cell interactions that may be important in a particular pathological state. Furthermore, it is well known in the art that cultured cells, over a period time, lose phenotypic characteristics associated with their normal counterpart cell type. Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p4) teach that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro*). Further, Dermer (Bio/Technology, 1994, 12:320) teaches that, "petri dish cancer" is a poor representation of malignancy, with characteristics

profoundly different from the human disease. Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not. Yet normal or malignant cells *in vivo* are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions.

There is insufficient evidence or nexus that would lead the skilled artisan to predict the ability to treat a solid tumor with an antibody containing only on CDR that specifically binds to a protein having the amino acid sequence of SEQ ID No. 2. The specification does not teach a therapeutic antibody containing fewer than 6 CDR's (3 heavy chain and 3 light chain).

In view of the lack predictability of the art to which the invention pertains, undue experimentation would be required to practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed methods absent working examples providing evidence which is reasonably predictive that the claimed methods are effective for treating a solid tumor, commensurate in scope with the claimed invention.

Claim Rejections - 35 USC § 102

15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

16. Claims 15-21 are rejected under 35 U.S.C. 102(b) as being anticipated by Morin, et al. (US PG PUB 2003/0211498, PCT filed April 4, 2001).

The claims recite a therapeutic method comprising as an active ingredient an antibody that specifically binds to a protein having the amino acid sequence set forth in SEQ ID No. 2 or an antibody fragment that maintains the antibody activity, in which said antibody is a monoclonal antibody, in which said antibody is a chimeric antibody comprising the constant region of a human antibody and the variable region of a mouse antibody, in which said antibody is a humanized antibody comprising the complementarity determining region of a mouse antibody and the framework region and the constant region of a human antibody, in which said antibody is a human antibody, in which said antibody fragment is a Fab, Fab', $F(ab')_2$ or Fv fragment, in which said solid tumor is breast cancer or ovarian cancer.

Morin, et al. teach an antibody that specifically recognizes bone marrow stromal antigen (BST-2) the sequence of which is identical to the sequence of the protein of SEQ ID No. 2 in the instant application (see sequence alignment). Morin, et al. teach the tumor marker genes of the invention can be employed as therapeutic targets for the treatment or prevention of ovarian cancer (paragraph 72). Morin, et al. teach the

monoclonal antibody may be humanized or human antibodies and may include fragments such as Fv, Fab, Fab' or other antigen-binding subsequences of antibodies (paragraph 84). Since the claims do not recite the specific therapeutic method steps (see 112, second paragraph above), and ovarian cancer is a solid tumor, all the limitations of the claims have been met.

Conclusion

17. No claims are allowed.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne M. Gussow whose telephone number is (571) 272-6047. The examiner can normally be reached on Monday - Friday 8:30 am - 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Anne M. Gussow

July 9, 2007

LARRY R. HELMS, PH.D.
SUPERVISORY PATENT EXAMINER